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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/66, 31/675</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 95/28936</b> <b>(43) International Publication Date:</b> 2 November 1995 (02.11.95)
<b>(21) International Application Number:</b> PCT/US95/04498 <b>(22) International Filing Date:</b> 17 April 1995 (17.04.95)  <b>(30) Priority Data:</b> 230,670 21 April 1994 (21.04.94) US  <b>(60) Parent Application or Grant</b> <b>(63) Related by Continuation</b> US 230,670 (CON) Filed on 21 April 1994 (21.04.94)  <b>(71) Applicant (for all designated States except US):</b> MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).  <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> YATES, Ashley, J. [GB/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).  <b>(74) Common Representative:</b> MERCK & CO., INC.; Patent Dept., 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		<b>(81) Designated States:</b> AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TT, UA, US, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> USE OF BISPHOPHONATES FOR INHIBITING BONE RESORPTION FOLLOWING IMPLANTATION OF ORTHOPEDIC PROSTHESIS		
<b>(57) Abstract</b>		
Disclosed is a therapy for treating and for preventing periprosthetic bone loss by the administration of a bisphosphonate bone resorption inhibitor, e.g., alendronate, in patients who have an orthopedic implant device.		

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## TITLE OF THE INVENTION

USE OF BISPHOSPHONATES FOR INHIBITING BONE RESORPTION FOLLOWING IMPLANTATION OF ORTHOPAEDIC PROSTHESIS.

### 5 FIELD OF THE INVENTION

The instant invention relates generally to the use of alendronate to prevent periprosthetic bone loss in patients having an orthopedic implant device.

### 10 BACKGROUND OF THE INVENTION

A major problem with patients who have orthopedic implant devices or joint prosthesis, such as hip replacements, is that many of these begin to fail after five years or so from the time that they are inserted. The failure rate increases exponentially with time so that many patients with an aging hip prosthesis (10 to 15 years), experience pain at the site of the implant and eventually require revision to the original procedure. Although initially this was considered to be a result of fragmentation of the cement substances utilized in older hip prostheses, the problem continues to be observed even in the newer devices which do not rely on the use of cement. A hallmark of these patients is that at the time they develop pain and loosening of the joint they have markedly increased bone turnover, especially bone resorption, in the bone immediately adjacent to the implant. Evidence for this bone turnover can be seen from the fact that bone scanning agents, which are bisphosphonates tagged with technetium, are often taken up at very high concentrations in these areas indicating that there may well be significant targeting of bisphosphonates to the periprosthetic bone.

There is a need in the art for localized controlled/extended release dosage forms of bone growth promotant since in the United States, there are approximately 5 million fractures and 265,000 prosthetic implants per year. Of this population, there is about a 20-30% failure rate within five years of the operation, requiring a repeat surgery and device implant.

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Normal bones are living tissues which undergo constant resorption and new bone formation, with the net effect of maintenance of a constant mineral balance. The dual process is commonly called "bone turnover". In normal growing bones, the mineral deposition exceeds the mineral resorption, whereas in certain pathological conditions, bone resorption exceeds bone deposition, for instance, due to malignancy or primary hyperparathyroidism, or in osteoporosis. In other pathological conditions the deposition of new bone may take place in undesirable amounts and areas leading to, e.g., heterotopic ossification, osteosclerosis, and Paget's disease which is a combination of an abnormal high bone resorption followed by an abnormal calcium deposition. With orthopedic implants, bone resorption may occur at an accelerated rate in the periprosthetic area leading to net bone loss.

Most of the currently available therapeutic agents for the treatment of osteoporosis, e.g., estrogens, act by reducing bone resorption in the osteoporotic patient. See the review article, "British Medical Bulletin" 46 (1), p. 94-112 (1990).

Bisphosphonates are also known in the art as bone resorption inhibitors.

Alendronate, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium trihydrate is a known bone resorption inhibitor and is described in U.S. Patents 4,922,007 and 5,019,651 (Merck).

Clodronate, (dichloromethylene)bisphosphonic acid disodium salt (Proctor and Gamble, is described in Belgium Patent 672,205 (1966) and its preparation is found in *J. Org. Chem* 32, 4111 (1967).

Tiludronate, ([4-chlorophenyl]thiomethylene)-bisphosphonic acid (Sanofi) is described in U.S. Patent 4,876,248 issued October 24, 1989.

YM 175 ([cycloheptylamino)methylene]bisphosphonic acid, disodium salt) by Yamanouchi is described in U.S. Patent 4,970,335 issued November 13, 1990.

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BM 21.0995 (1-Hydroxy-3-(methylpentylamino)-propylidene-bisphosphonate) by Boehringer-Mannheim - is described in U.S. Patent 4,927,814 issued May 22, 1990.

5 A study by Proctor and Gamble (Norwich Eaton Pharmaceuticals) using risedronate, whose chemical name is sodium trihydrogen [1-hydroxy-2-(3-pyridinyl)ethylidene]bisphosphonate, in combination with estrogen showed a positive effect on bone loss in ovariectomized rats (published in Abstracts 731 and 732 at the Fall 1992 ASBMR meeting in Minnesota).

10 The article, "J. Clin. Invest.", Jan. 1992, 89 (1), p. 74-78 by J. Chow *et al.*, describes the effect of estrogen on ovariectomized rats in which bone resorption was suppressed by pamidronate whose chemical name is 3-amino-1-hydroxy propylidene-bisphosphonic acid disodium salt. They concluded that estrogen inhibits bone resorption and also stimulates bone formation.

15 Another Proctor and Gamble compound, piridronate, [2-(2-pyridinyl)ethylidene]-bisphosphonic acid, monosodium salt is described in USP 4,761,406 as having bone resorption inhibition activity.

20 The article, "Monatshefte" 99, 2016 (1968) by F. Kasporet describes the synthesis of etidronate, (1-hydroxyethylidene)-bisphosphonic acid, disodium salt, (Proctor and Gamble).

25 However, the above cited art does not suggest or describe the use of a bisphosphonate in situations to specifically prevent bone resorption in the periprosthetic bone area of an orthopedic implant device.

30 What is desired in the art is a therapy to optimally treat the bone resorption in the periprosthetic area of an implant device, i.e., the bone area which is in contact and close proximity to the device implant, to retard the loosening of the device and to alleviate the pain associated with this condition.

#### SUMMARY OF THE INVENTION

We have discovered that a bisphosphonate can be used in such patients for the prophylaxis and treatment of failure of joint

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prostheses, e.g., for the hip or knee. Long term administration of a relatively low dose of a bisphosphonate, e.g., alendronate, can prevent the periprosthetic bone resorption process and thereby maintain the integrity of the total structure.

5           The treatment can be further extended to patients with symptomatic failure of a joint prostheses or internal fixation device. Bisphosphonates, e.g., alendronate, are able to reverse the loosening of a prosthesis once it has occurred, and there is also some alleviation of the bone pain which accompanies this complication of joint replacement.

10           By this invention there is provided a method for treating and/or preventing (reducing the risk of) periprosthetic bone loss in a subject having an orthopedic implant device comprising administering to said subject a pharmaceutically effective dose of a bisphosphonate. The bisphosphonate applicable in the method includes: alendronate, 15 clodronate, tiludronate, YM 175, BM 21.0995, etidronate, risedronate, piridronate, pamidronate, or combinations thereof.

#### BRIEF DESCRIPTION OF THE FIGURE

20           The Figure illustrates the effects of alendronate on bone resorption at different concentrations, on the rat bone marrow ablation model in which bone is regenerated in the voided regions of the bone.

#### DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

25           The bisphosphonates described above are useful in the invention process. Preferred are residronate, clodronate, tiludronate and alendronate and particularly preferred is alendronate.

30           The method disclosed herein can be used to treat human subjects who have a prosthesis, i.e., a medical implant device.

          The method involves the administration of a bisphosphonate in an osteogenically effective amount to inhibit bone resorption in the periprosthetic bone area of a medical implant device.

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By the term "periprosthetic bone area" as used herein is meant the area of bone which is in contact with the medical implant device or in the immediate proximity thereof.

5 The term "inhibition of bone resorption" as used herein refers to prevention of bone loss, especially the inhibition of removal of existing bone either from the mineral phase and/or the organic matrix phase, through direct or indirect alteration of osteoclast formation or activity. Thus, the term "inhibitor of bone resorption" as used herein  
10 refers to agents that prevent bone loss by the direct or indirect alteration of osteoclast formation or activity.

The term "osteogenically effective" as used herein means that amount which decreases the turnover of mature bone. As used herein, an osteogenically effective dose is also "pharmaceutically effective."  
15

The term "subject" as used herein refers to a living vertebrate animal such as a mammal in need of treatment, i.e., in need of periprosthetic bone repair. The periprosthetic bone loss may arise in cases of systemic bone disease, as in osteoporosis (of any etiology), osteoarthritis, Paget's disease, osteomalacia, multiple myeloma and other  
20 forms of cancer.

The term "treatment" or "treating" as used herein shall mean (1) providing a subject with an amount of a bisphosphonate sufficient to act prophylactically on periprosthetic bone to prevent the development of a weakened and/or unhealthy state; and/or (2) providing a subject with a  
25 sufficient amount of a bisphosphonate so as to alleviate or eliminate a disease state and/or the symptoms of a disease state in the area of periprosthetic bone.

The methods of the invention are useful for treating defects and disorders in the periprosthetic area of bone which result in a  
30 weakened structure and/or pain.

In accordance with one method of use, the bisphosphonate may be administered to the periprosthetic bone area systemically either orally and/or parenterally, including subcutaneous or intravenous

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injection. Additionally, the bisphosphonate may be delivered in a slow release form from a suitable carrier.

5 In accordance with another method of use, the bisphosphonate may be administered locally to the specific periprosthetic area in need of bone growth or repair. Thus, the bisphosphonate may be implanted directly at the site to be treated, for example, by injection or surgical implantation in a sustained-release carrier. Suitable carriers include hydrogels, controlled- or sustained-release devices (e.g., an Alzet® minipump), polylactic acid, and collagen matrices. Presently preferred carriers are formulations of atelopeptide collagen containing particulate calcium phosphate mineral components, such combinations of homologous or xenographic fibrillar atelopeptide collagen (for example, Zyderm® Collagen Implant, available from Collagen Corporation, Palo Alto, Calif.) with hydroxapatitetricalcium phosphate (HA-TCP, available from Zimmer, Inc., Warsaw, In.). It is presently preferred to administer implant compositions containing alendronate in a collagen/mineral mixture implant.

20 Bisphosphonate delivered in sustained-release vehicles is useful for improving implant fixation, for example, for improving in growth of new bone into a metal prosthesis in joint reconstruction or orthopedic implants.

25 Alternatively, orthopedic implants can be coated with bisphosphonate to enhance attachment of the implant device to the bone at the time of the implant operation.

30 In general, implant devices may be coated with a bisphosphonate as follows. The bisphosphonate is dissolved at a concentration in the range of 0.01 µg/ml to 200 mg/ml in phosphate-buffered saline (PBS) containing 2 mg/ml serum albumin. The porous end of an implant is dipped in the solution and is airdried (or lyophilized) or implanted immediately into the bony site. The viscosity of the coating solution is increased, if desired, by adding hyaluronate at a final concentration of 0.1 mg/ml to 100 mg/ml or by adding other pharmaceutically acceptable excipients. Alternatively, the solution containing the bisphosphonate, is mixed with collagen gel or human



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collagen (e.g., Zyderm® Collagen Implant, Collagen Corp., Palo Alto, Calif.) to a final collagen concentration of 2 mg/ml to 100 mg/ml to form a paste or gel, which is then used to coat the porous end of the implant device. The coated implant device is placed into the periprosthetic bony site immediately or is airdried and rehydrated with PBS prior to implanting, with the objective of maximizing new bone formation into and around the implant while minimizing the ingrowth of soft tissue into and around the implant site.

Pharmaceutical formulations of the invention which include a bisphosphonate inhibitor of bone resorption for administration will generally include an osteogenically effective amount of the bisphosphonate to promote bone growth, in addition to a pharmaceutically acceptable excipient. Suitable excipients include most carriers approved for parenteral administration, including water, saline, Ringer's solution, Hank's solution, and solutions of glucose, lactose, dextrose, ethanol, glycerol, albumin, and the like. These compositions may optionally include stabilizers, antioxidants, antimicrobials, preservatives, buffering agents, surfactants, and other accessory additives. The bisphosphonate inhibitor of bone resorption may also be delivered in a sustained release form from a suitable carrier.

A presently preferred vehicle comprises phosphate-buffered saline (PBS) or isotonic citrate buffer. A thorough discussion of suitable vehicles for parenteral administration may be found in E. W. Martin. "Remington's Pharmaceutical Sciences" (Mack Pub. Co., current edition sections relating to the excipient vehicles and formulating being incorporated herein by reference to disclose such). Such formulations are generally known to those skilled in the art and are administered systemically to provide systemic treatment.

The precise dosage of bisphosphonate necessary will vary with the age, size, sex and condition of the subject, the nature and severity of the disorder to be treated, and the like; thus, a precise effective amount cannot be specified in advance and will be determined by the caregiver. However, appropriate amounts may be determined by routine experimentation with animal models, as described below. In general

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terms, an effective dose for biphosphonate is about 1.5 to 3000 µg/kg per day of body weight and preferably about 10 µg/kg to about 200 µg/kg per day of body weight. A particularly preferred dosage is 10 mg per day per person.

Effective doses for local administration will be about 0.001 µg to 1 mg per application site.

The pharmaceutical compositions according to the present invention containing bisphosphonate may be prepared for use in the form of capsules or tablets or in solution for oral administration or for systemic use. The compositions are advantageously prepared together with inert carriers such as sugars (saccharose, glucose, lactose), starch and derivatives, cellulose and derivatives, gums, fatty acids and their salts, polyalcohols, talc, aromatic esters.

Some typical pharmaceutical formulations containing alendronate, 4-amino-1-hydroxybutane-1,1-diphosphonic acid monosodium salt trihydrate, are shown here below:

ALENDRONATE TABLETS (WHITE), 200 MG

<u>INGREDIENT</u>	<u>COMPOSITION IN MG/TABLET</u>			
	<u>2.5 mg*</u>	<u>5.0 mg*</u>	<u>10.0 mg*</u>	<u>40.0 mg*</u>
Alendronate	3.26	6.55	13.05	51.21
Lactose NF Anhydrous	113.74	110.45	103.95	64.79
Microcrystalline Cellulose NF	80.0	80.0	80.0	80.0
Magnesium Stearate Impalpable NF	1.00	1.00	1.00	1.00
Croscarmellos Sodium NF Type A	2.00	2.00	2.00	2.00

\* Taken as the anhydrous monosodium salt-active ingredient.

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OPERCOLATED CAPSULES

		1	2
5	Alendronate	mg 6.5	mg 2.5
	Lactose	110.0	110.0
	Avucek Ph101	80.0	80.0
	Aldisol/NF Type A	2.0	2.0
10	Magnesium Stearate	1.0	1.0
	Total		Total
	Weight	202.5	Weight 197.5

EFFERVESCENT  
GRANULATES

15	Alendronate	mg 5.0
	Anhydrous Sodium Carbonate	12.0
	Sodium Bicarbonate	63.0
20	Anhydrous Citric Acid	110.0
	Sodium Saccharinate	5.0
	Saccharose	493.0
	Dehydrated Lemon Juice	55.0
	Natural Essence of Lemon	2.0
25	Total Weight	748

FORMULATIONS  
SUITABLE FOR INJECTION

30	Alendronate	mg 0.5	mg 1.00
	Sodium Hydroxide	0.25	0.25
	Sodium Chloride	8.40	16.30
	Purified Water q h	ml 1.0	ml 12.0

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Bisphosphonate drugs which prevent bone loss and/or add back lost bone can be evaluated in the ovariectomized rat. This animal model is well established in the art (see, for example, Wronski, *et al.*, (1985) "Calcif. Tissue Int." 37:324-328; Kimmel, *et al.*, (1990) "Calcif. Tissue Int." 46:101-110; and Durbridge, *et al.*, (1990) "Calcif. Tissue Int." 47:383-387; these references are hereby incorporated in their entirety). Wronski, *et al.*, ((1985) "Calcif. Tissue Int." 43:179-183)) describe the association of bone loss and bone turnover in the ovariectomized rat. Bisphosphonate drugs applicable in the instant invention are active in this assay.

#### EXAMPLE

##### Alendronate Effects on Bone Formation and Resorbability of Bone Formed During Alendronate Treatment

To study the effects of alendronate during rapid bone formation, a modified bone marrow ablation model in the rat described in *J. Bone Miner. Res.* Vol. 8, pp. 379-388 (1993) by L. J. Suva *et al.*, was used. In the rat, extraction of bone marrow (ablation) from a long bone results in rapid bone formation which fills 25% of the marrow cavity with cancellous bone (Cn) within 6 to 7 days. This bone is then fully resorbed (replaced) within the next 15 days. When rats were orally treated with 1, 2, 8 or 40  $\mu\text{g/kg}$  alendronate day s.c. for 6 days, post-ablation, there was no difference in bone volume at 7 days (See the Figure), indicating that alendronate has no detectable effect on bone formation. In the Figure, Cn-BV/TV% represents cancellous bone volume divided by total structure volume; SEM represents standard error of the mean; ALN is alendronate; Fisher PLSD is a standard statistical least squares technique. After treatment was stopped, the amount of bone remaining in the marrow cavity at the various doses was examined at 4, 14, 24 and 54 days later. For an alendronate dose of 1  $\mu\text{g/kg}$ , bone was completely resorbed at 14 days, no different from controls. At 2  $\mu\text{g/kg/day}$ , bone was also completely resorbed 24 days after cessation of treatment. At 8 and 40  $\mu\text{g/kg/day}$ , bone was also resorbed, albeit more slowly, resulting in a

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retention of about 33% and 50%, respectively, at 54 days (See the Figure). These findings show that, at levels much higher than a human dose, there is no interference at all with bone formation in this model, and that bone formed at these doses is fully resorbable, albeit more slowly than occurs with lower doses.

This data is consistent with the method of administering a bisphosphonate, e.g., alendronate, to a patient's periprosthetic bone area to prevent bone resorption and a weakening at the site of the medical implant device. The slowing of the rate of bone resorption, but not its complete inhibition, is predicted to be associated with an improvement in the local bone balance in the periprosthetic bone which would provide greater integrity to the overall bone and prosthesis structure.

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WHAT IS CLAIMED IS:

- 5 1. A method for treating and/or preventing periprosthetic bone resorption in a subject having an orthopedic implant device, comprising administering to said subject a pharmaceutically effective amount of a bisphosphonate bone resorption inhibitor.
2. The method of Claim 1 wherein the subject is human.
- 10 3. The method of Claim 1 wherein the treatment is prophylactic.
4. The method of Claim 1 wherein said bone resorption inhibitor is administered by an oral dosage form.
- 15 5. The method of Claim 1 wherein said bone resorption inhibitor is administered parenterally.
- 20 6. The method of Claim 5 wherein said bone resorption inhibitor is administered parenterally at the site of the periprosthetic bone.
- 25 7. The method of Claim 1 wherein said bisphosphonate bone resorption inhibitor is selected from the group consisting of: alendronate, clodronate, tiludronate, YM 175, BM 21.0995, etidronate, risedronate, piridronate, pamidronate, or a mixture thereof.
- 30 8. The method of Claim 7 wherein said bone resorption inhibitor is alendronate.

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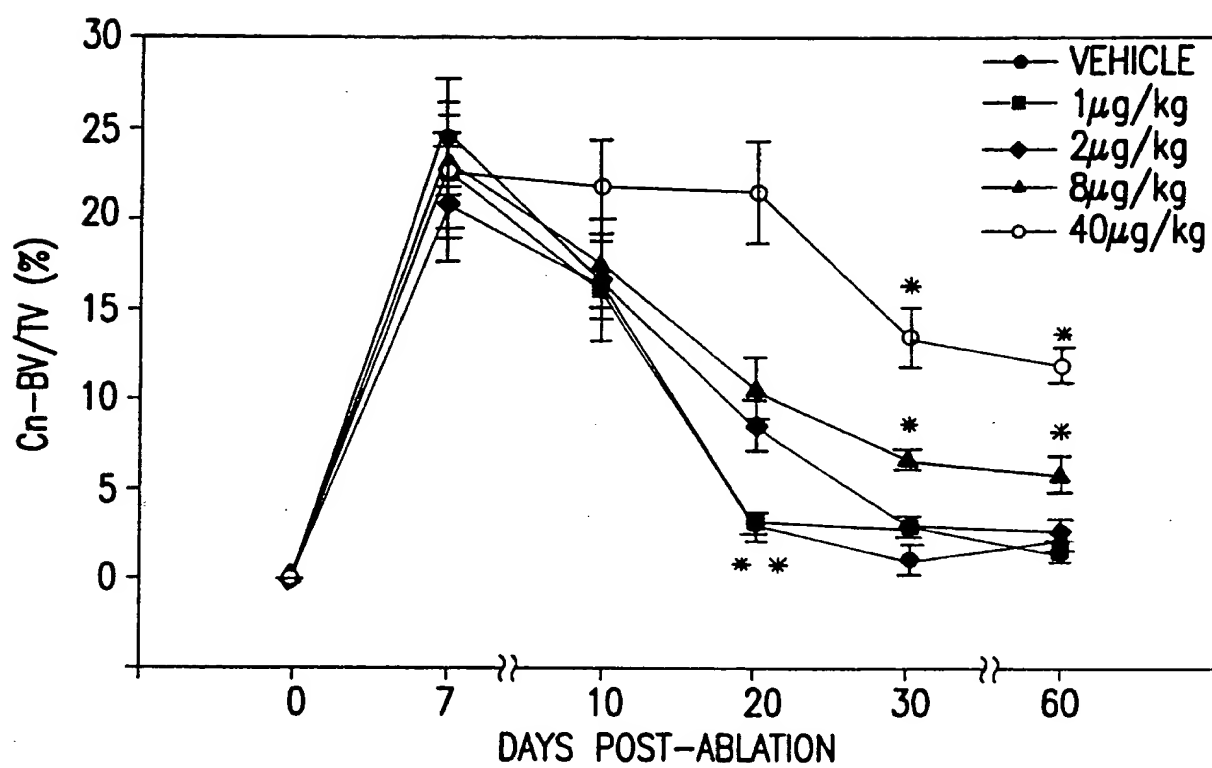


FIG.1

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 95/04498

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 6 A61K31/66 A61K31/675

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO-A-94 21266 (LEIRAS OY) 29 September 1994 see the whole document ---	1-8
P,X	WO-A-94 23770 (LEIRAS OY) 27 October 1994 see the whole document ---	1-8
P,X	WO,A,94 14455 (MERCK & CO. INC.) 7 July 1994 see page 9, line 5-30 ---	1-8
X	US,A,4 753 652 (LANGER ET AL) 28 June 1988 see claims 4-6,31 ---	1-3,6,7
X	EP-A-0 094 714 (THE PROCTER & GAMBLE COMPANY) 23 November 1983 see the whole document especially page 5, line 9-10 ---	1-7
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search

25 July 1995

Date of mailing of the international search report

Name and mailing address of the ISA

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## INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE MEDLINE US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US AN:93213656, see abstract & ANN ITAL MED INT, vol. 7, no. 3 suppl., July 1992 - September 1992 pages 137S-153S, PASSERI, M. ET AL 'ESPERIENZE DI TRATTAMENTO DEL DOLORE CRONICO DEL RACHIDE NELLA OSTEOPOROSI INVOLUTIVA' ---	1,2,5,7, 8
A	Z. ORTHOP., vol. 126, no. 3, 1988 pages 314-325, DUSTMANN, H. O. ET AL 'ERFAHRUNGEN MIT DER ZEMENTFREIEN IMPLANTATION DER ZWEYMÜLLER/ENDLER- UND ZWEYMÜLLER-HÜFTGELENKS-TOTALENDOPROTHESE' see the whole document ---	1-8
A	METABOLIC BONE DISEASE AND RELATED RESEARCH, vol. 3, no. 4&5, 1981 pages 337-342, FINERMANN, G.A.M. ET AL 'HETEROTOPIC OSSIFICATION FOLLOWING HIP REPLACEMENT OR SPINAL CORD INJURY. TWO CLINICAL STUDIES WITH EDHP.' see the whole document -----	1-8

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although all claims are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compounds.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int: nal Application No

PCT/US 95/04498

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